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Evidence for Locus Heterogeneity in Human Autosomal Dominant Split Hand/Split Foot Malformation

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Summary

Split hand/split foot (SHSF; also known as *ectrodactyly*) is a human developmental disorder characterized by missing central digits and other distal limb malformations. An association between SHSF and cytogenetically visible rearrangements of chromosome 7 at bands q21-q22 provides compelling evidence for the location of a causative gene at this location, and the locus has been designated *SHFD1*. In the present study, marker loci were localized to the SHFD1 critical region through the analysis of somatic cell hybrids derived from individuals with SHSF and cytogenetic abnormalities involving the 7q21-q22 region. Combined genetic and physical data suggest that the order of markers in the SHFD1 critical region is cen–D7S492 – D7S527 – (D7S479 – D7S491) – SHFD1 – D7S554 – D7S518–qter. Dinucleotide repeat polymorphisms at three of these loci were used to test for linkage of SHSF to this region in a large pedigree that demonstrates autosomal dominant SHSF. Evidence against linkage of the SHSF gene to 7q21-q22 was obtained in this pedigree. Therefore, combined molecular and genetic data provide evidence for locus heterogeneity in autosomal dominant SHSF. We propose the name *SHSF2* for this second locus.

Introduction

Split hand/split foot (SHSF) is a human developmental disorder characterized by a deep median cleft in the hands and feet, missing digits, and fusion of remaining digits (fig. 1). This condition, also known as *ectrodactyly* or *lobster claw deformity* (MIM 183600; OMIM 1993), is usually inherited in an autosomal dominant fashion. A consistent association between SHSF and deletions of chromosome 7 at bands q21-q22 provides compelling evidence for the location of a causative gene in this region (Del Porto et al. 1983; Pfeiffer 1984; Tajara et al. 1989; Morey and Higgins 1990; Rivera et al 1991; Roberts et al. 1991), and the locus has been designated *SHFD1* (Cuticchia et al 1993). Further support for localization of the SHFD1 gene to this region is provided by reports of patients with cytogenetic translocations and inversions involving breakpoints in bands 7q21-q22 (Sharland et al. 1991; Akita et al. 1993; Genuardi et al. 1993; Naritomi et al. 1993).

Through analysis of somatic cell hybrids (SCHs) derived from SHSF patients with cytogenetic abnormalities, the *SHFD1* locus has recently been mapped to one of 10 physically defined intervals on human chromosome 7 (Scherer et al. 1994). SHSF-associated translocation breakpoints in four unrelated individuals were found to lie within the smallest region of overlap defined by three SHSF-associated deletions. The critical SHFD1 region was estimated to be ~1,000 kb. In the present study we identified polymorphic marker loci in the SHSF critical region that flank an SHSF-associated translocation breakpoint. These markers were used to test for genetic linkage, of markers in the SHFD1 critical region, to the SHSF phenotype in an autosomal dominant pedigree. We found evidence against linkage of the SHSF locus to markers in the SHFD1 region in this family. Thus, these data provide evidence for locus heterogeneity in dominant SHSF, implying that mutations in at least two separate autosomal genes can result in this distinctive human developmental disorder.

Subjects and Methods

A multigenerational kindred with SHSF was analyzed by genetic linkage analysis. Transmission of SHSF in the family (SF701) was consistent with an autosomal dominant pattern of inheritance (fig. 2).

There is no family history of consanguinity. Although there was no male-to-male transmission, four of the six affected individuals were female, and there were no differences, in phenotypic severity, between males and females, thus making an X-linked mode of inheritance highly unlikely. There is no evidence of reduced penetrance. The phenotype of the affected individuals is typical of classic

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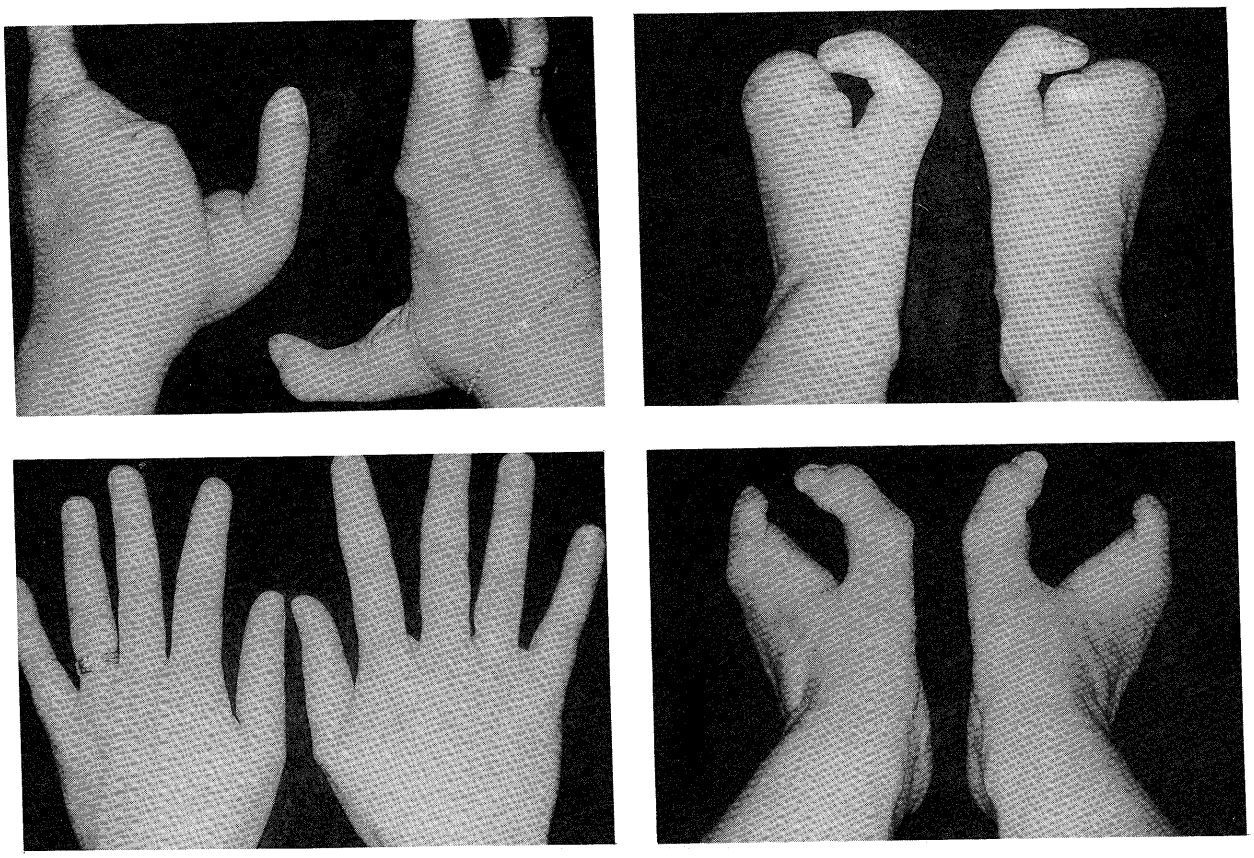

Figure 1 SHSF phenotype. Hands (*left*) and feet (*right*) of two affected individuals from the pedigree analyzed are depicted. Note that the individual in the top two photographs shows characteristic findings of median cleft, missing digits, and syndactyly in both hands and feet, while her daughter, in the bottom two photographs, has normal hands, illustrating the variable expressivity typically seen in this disorder.

SHSF, with a deep median cleft in the hands and feet, missing digits, and fusion of remaining digits (fig. 1). Typical variable expressivity is present, with some individuals more severely affected than others. Cell lines were established for all family members and were used as a source of DNA (Bell et al. 1981; Neitzel 1986). Phenotypic characteristics of patients with SHSF and cytogenetic rearrangements in the 7q21-q22 region, as well as construction of SCHs carrying the derivative chromosome 7, have been described in the accompanying paper (Scherer et al. 1994).

Six loci—D7S527, D7S479, D7S554, D7S492, D7S491, and D7S518—were analyzed to delineate the SHFD1 critical region (Weissenbach et al. 1992). Oligonucleotides to amplify dinucleotide polymorphisms at these loci (AFM248vd9, AFM036xg5, AFM248te5, AFM158xa1, AFM151xf10, and AFM225xg9, respectively) were obtained from Research Genetics, Huntsville. Polymorphisms were amplified by PCR using radiolabeled primer (Maniatis et al. 1982, p. 124; Weber et al. 1991). Products were analyzed by electrophoresis on 5% Long Ranger gels (JT Baker) and were visualized by autoradiography.

Linkage analyses were performed with the LIPED program (Ott 1974), assuming autosomal dominant inheri-

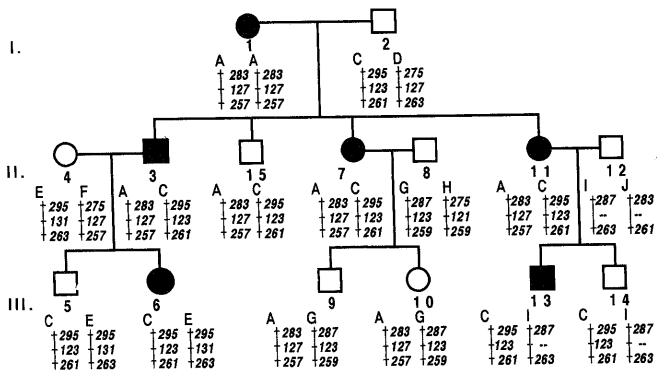

Figure 2 Pedigree and haplotypes of SHSF family SF701. The pedigree is diagrammed with symbols indicating males (□ and ■) and females (○ and ●) and affected (● and ■) and unaffected (○ and □). Below each symbol is the individual number for each family member tested; generations are designated by Roman numerals. Haplotypes for each locus within the 7q21-q22 chromosomal segment (*vertical lines*) are identified by the letters A–J, with the individual genotypes at each locus listed as size (in bases) of allele. Loci in each haplotype are D7S527 (*top*), D7S479 (*middle*), and D7S554 (*bottom*). Blank spaces represent samples that did not amplify but that do not affect interpretation.

tance with a disease-allele frequency of .0001. Since the actual penetrance in family SF701 is unknown, LOD scores were calculated under two models. The first model assumed a fixed penetrance of .70, which is the value usually given in the literature for this disorder (Thompson et al. 1991). The more stringent, second model assumed a fixed penetrance of .01, which effectively excludes the disease genotypic data contributed by unaffected individuals who may be nonpenetrant.

Results

To identify polymorphic loci located within the SHFD1 critical region, we analyzed SCHs derived from individuals with SHSF and cytogenetic abnormalities. In figure 3, six loci in the 7q21-q22 region were evaluated for their location with respect to SHSF-associated deletions and an SHSF-associated translocation breakpoint. D7S527, D7S479, D7S491, and D7S554 were all found to lie within the SHFD1 critical region, since primers representing these loci failed to produce a PCR product from SCHs that contain a human chromosome 7 that bears an SHSF-associated deletion (fig. 3, lanes 6–8). Note that lane 8 of figure 3 represents an SCH derived from a patient with the smallest reported SHSF-associated deletion (Roberts et al. 1991; Scherer et al. 1994). The loci within the SHFD1 critical region were also evaluated for their location with respect to the breakpoint in a patient with both SHSF and a balanced translocation. Loci D7S527, D7S479, and D7S491 were found to be proximal to the translocation breakpoint, since a signal is evident only in lane 4 of figure 3, while locus D7S554 was found to be distal to the translocation breakpoint, since a signal was evident only in lane 5 of figure 3. Thus, four loci were identified that lie within the SHFD1 critical region and flank an SHSF-associated translocation breakpoint (and therefore presumably flank the SHFD1 gene). These physical results, in conjunction with previous genetic mapping (Weissenbach et al. 1992), suggests the following order: cen–D7S492–D7S527–(D7S479–D7S491)–SHFD1–D7S554–D7S518–qter, with an ~2-cM interval between D7S527 and D7S554.

Markers found to lie within the SHFD1 critical region were employed in linkage analysis of a large kindred with autosomal dominant SHSF. The haplotypes derived from the genotypes at three polymorphic marker loci flanking SHFD1 (D7S527, D7S479, and D7S554) are shown in figure 2. The affected matriarch of the family (I-1) was homozygous at all three loci (designated as haplotype "A/A"). However, the A haplotype did not cosegregate with the SHSF phenotype in her two affected grandchildren. Affected grandchild III-6 received the grandpaternal haplotype (C) from her affected father, II-3, while the other haplotype (E) was from the mother, II-4. Affected grandchild III-13 received from his affected mother, II-11, the same grandpaternal haplotype (C) as was found in his affected cousin and received the other haplotype (I) from his father, II-12. These results provide strong evidence that the gene responsible for the SHSF phenotype in this family is not localized within the SHFD1 critical region at 7q21-q22.

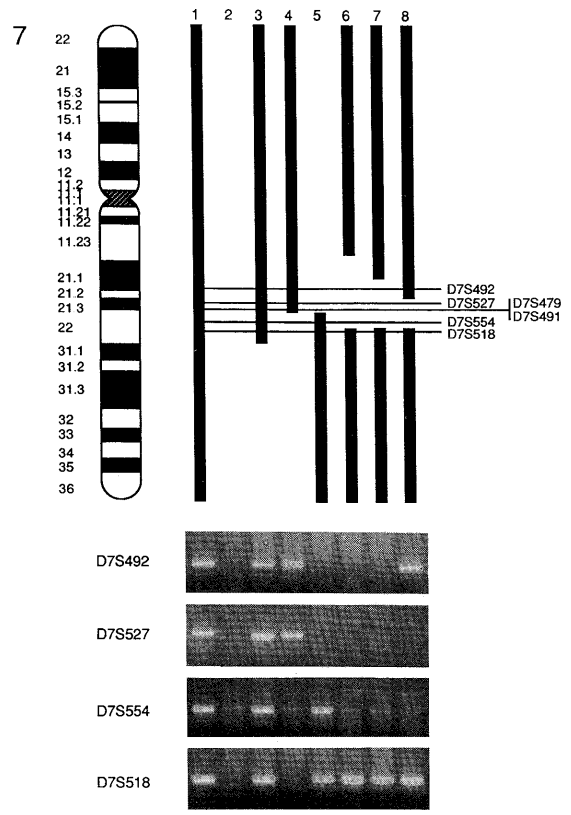

Figure 3 Localization of marker loci with respect to SHSF-associated deletions and a translocation breakpoint. *Top*, Ideogram of human chromosome 7. Numbers 1–8 represent SCHs; and the vertical bars indicate the proportion of human chromosome 7 contained in each cell line. Hybrid 1 is a control containing an entire human chromosome 7; hybrid 2 is a control not containing any human chromosome 7 material; hybrid 3 is a control derived from an individual without SHSF who has a terminal deletion of 7q (i.e., 7q31.1-qter); hybrid 4 is a cell line derived from an individual with SHSF and a balanced translocation (46XXt(7:12)(q22.1:q24.2) containing only human chromosome 7 material proximal to the translocation breakpoint; hybrid 5 is a cell line derived from the same individual as is hybrid 4 but containing only chromosome 7 material distal to the translocation breakpoint; and hybrids 6–8 are cell lines derived from individuals with SHSF and interstitial deletions of chromosome 7; each hybrid contains only the deletion-bearing human chromosome 7. *Bottom*, PCR analyses of marker loci on human chromosome 7q. Products of amplification of DNA derived from each SCH are shown in vertical lanes below the corresponding hybrid diagram. Locations of each locus amplified (D7S492, D7S527, D7S554, and D7S518) are depicted in relation to the breakpoints in the hybrid diagrams above (results of amplification of D7S479 and D7S491 are not shown, since they gave results identical to those for locus D7S527). The patients from whom SCHs were derived have been described elsewhere: hybrid 1, patient JSR-17S (Scherer et al. 1993); hybrid 3, patient 1CF2/5/K016 (Scherer et al. 1993); hybrids 4 and 5, patient T1 (Scherer et al. 1994); hybrids 6–8, patients D1–D3, respectively (Scherer et al. 1994).

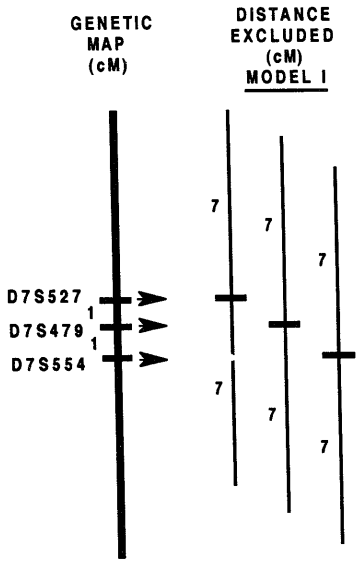

Figure 4 Exclusion distances from two-point linkage analysis. The genetic map is diagrammed by the thicker vertical line on the left side of the figure; the translocation breakpoints are located between flanking markers D7S479 and D7S554 (see fig. 2). Genetic distances (in cM) (Kosambi 1944) excluded around each locus (LOD score <-2.0) by two-point analysis are indicated by the thinner vertical lines.

Pairwise LOD scores between SHSF and D7S527, D7S479, and D7S554 were calculated under two models that assume a penetrance of either .7 or .01. The maximum two-point LOD scores under both models were 0.00 at a recombination fraction (θ) of .5. Under a penetrance of .7 (model 1), a LOD score of -2.00, which provides significant evidence against linkage, was obtained at a $\theta = .07$, for each pairwise comparison. These data provide strong evidence to exclude the SHSF gene from within 7 cM on either side of each of these three loci. Combining these data with the known genetic map of this segment of chromosome 7 demonstrates that the SHSF gene is unlikely to lie in a 16-cM region spanning the entire SHFD1 critical region (fig. 4). Under a penetrance of .01 (model II), a two-point LOD score of -2.00 at $\theta = .04$ was obtained for each locus (table 1). Calculations from this more conservative model provide strong evidence to exclude the gene responsible for the phenotype in this family from within 4 cM either side of each of these three loci or a 10-cM interval spanning the entire SHFD1 critical region. Therefore, these results provide strong evidence that the SHFD1 critical region at 7q21-q22 is not the location of the SHSF gene in this family.

Discussion

Cytogenetic and molecular data support the unambiguous assignment of a locus for SHSF at 7q21-q22; this locus has been designated *SHFD1*. Linkage analysis with physically localized markers now suggests that genetic heterogeneity exists within the autosomal dominant form of SHSF, providing evidence for another autosomal locus (location as yet unknown). Furthermore, the previous report of a single large Pakistani pedigree in which SHSF is transmitted as an X-linked trait (linked to Xq26.1) demonstrates that mutations in yet another gene can result in this condition (Ahmad et al. 1987; Faiyaz-ul-Haque et al. 1993). Therefore, the current data suggest that the SHSF phenotype can result from disruption of any one of at least three distinct loci, all of which are presumably involved in some aspect of limb development. Additional locus heterogeneity might be suggested by several reports in the literature that are consistent with autosomal recessive inheritance of SHSF (Ray 1970; Freire-Maia 1971; Verma et al. 1976). However, these claims are difficult to evaluate in light of the well-documented reduced penetrance observed in this condition. In addition, the phenotype of the family in the latter report is unclear and bears some resemblance to the Cenani-Lenz type of syndactyly (Pfeiffer and Meisel-Stosiek 1982).

In this family, evidence that the causative gene for the SHSF phenotype is excluded from the SHFD1 critical region is particularly strong, since the markers that were used for this study reside within the critical region and flank an SHFD1-associated translocation breakpoint. Thus a double crossover within a 1-cM region in two individuals would be required to explain the results if a mutation in *SHFD1* were responsible for the phenotype in this family. The maximum combined probability of these two events is 6.25×10^{-10}. Distances excluded by the two-point analyses between the SHSF phenotype and each marker locus spanned the entire critical region in both model I (70% penetrance) and the more stringent model II (1% penetrance). It is formally possible that the chromosomal rearrangements found in association with SHSF cause the characteristic phenotype by effects on a distant locus that is genetically unlinked to the site of the translocation breakpoints. In this manner one might still postulate only a single autosomal SHSF gene. However, such "position effects" would have to be manifest at a considerable genetic and physical distance. Cloning and characterization of the breakpoint region at 7q21-q22 should clarify this issue.

The SHSF phenotype in the family studied here is indistinguishable from either SHSF associated with disruption of the 7q21-q22 region or the X-linked form of the disorder. Thus, the finding of locus heterogeneity has implications for genetic counseling, as well as for linkage studies that aim to localize the gene(s) responsible for SHSF. It will be important to use single large pedigrees for linkage analysis, exclude linkage to 7q21-q22 in the pedigrees analyzed, or identify characteristics that set SHFD1 families apart from other SHSF families. At present, no such distinguishing features are apparent.

Table 1

Pairwise LOD Scores between SHFD1 and Chromosome 7q21-22 Loci

Locus	LOD Scores at θ = .001	.05	.10	.15	.20	.30	.40
Model I (penetrance = .70):							
D7S527	−3.91	−2.22	−.157	−1.18	−.89	−.48	−.20
D7S479	−3.91	−2.22	−1.57	−1.18	−.89	−.48	−.20
D7S554	−3.91	−2.22	−1.57	−1.18	−.89	−.48	−.20
Model II (penetrance = .01):							
D7S527	−2.51	−1.90	−1.37	−1.04	−.79	−.44	−.19
D7S479	−2.51	−1.90	−1.37	−1.04	−.79	−.44	−.19
D7S554	−2.51	−1.90	−1.37	−1.04	−.79	−.44	−.19

There are reports in the literature of patients with cytogenetic abnormalities and SHSF that may suggest a location for the other autosomal SHSF locus (or loci). Two reports of patients with SHSF and abnormalities of chromosome 6 exist. In one case, an SHSF patient had an interstitial deletion of q16-q22.3 on chromosome 6 (Braverman et al. 1993). In another case, a patient with ectrodactyly has an unbalanced 6;13 translocation with a breakpoint at 6q21 (Viljoen and Smart 1993). In addition, the recent report of an interstitial deletion in chromosome 2 (2q24.2-q31.1) in a patient with ectrodactyly suggests another candidate gene region (Boles et al. 1993). Thus, markers in either of these general regions might be expected to demonstrate linkage with some ectrodactyly families.

It should be noted that several SHSF patients with cytogenetic abnormalities in the 7q21-q22 region also have other findings, such as bifid uvula (Naritomi et al. 1993) and cleft palate (Pfeiffer 1984). These abnormalities are characteristic of another autosomal dominant disorder with many similarities to SHSF, the EEC syndrome (*e*ctrodactyly, *e*ctodermal dysplasia, and *c*lefting) (Rodini and Richieri-Costa 1990), and suggest that different mutations at the same locus may result in either EEC or isolated SHSF. Alternatively, EEC and SHSF may result from disruption of distinct but tightly clustered developmental genes. Finally, EEC might be the result of a contiguous-gene deletion syndrome in this region. Additional support for the possibility that mutations within or near the *SHFD1* locus are responsible for EEC is derived from two reports of individuals with the EEC syndrome who have translocation breakpoints in 7q (Hasegawa et al. 1991; Akita et al. 1993; Fukushima et al. 1993). It should be possible to investigate the relationship between SHSF and EEC by performing genetic linkage studies of EEC families with marker loci in the 7q21-q22 region. The current data, which localized marker loci within the SHFD1 critical region, should be of considerable utility in such studies.

Finally, we propose that the SHSF locus at 7q21-q22 be designated *SHSF1* and that the former nomenclature, which employed the designation *SHFD1* (split hand/split foot deformity) be changed to reflect the fact that this developmental disorder is not a deformity but is a malformation. Accordingly, we designate the second autosomal locus, which is as yet not mapped, as *SHSF2*.

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